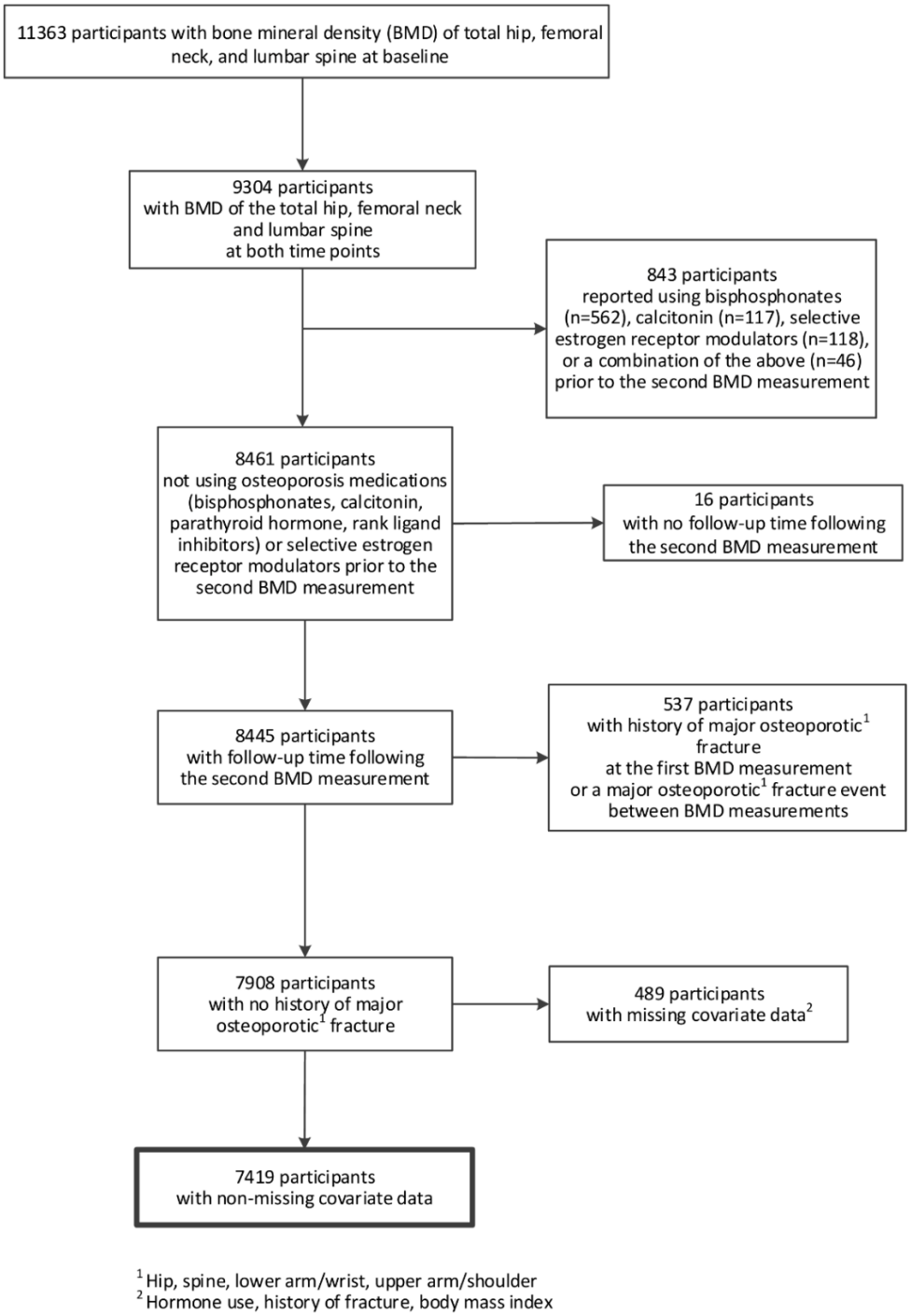
Supplementary Online Content

Crandall CJ, Larson J, Wright NC, et al. Serial bone density measurement and incident fracture risk discrimination in postmenopausal women. *JAMA Intern Med*. Published online July 27, 2020. doi:10.1001/jamainternmed.2020.2986

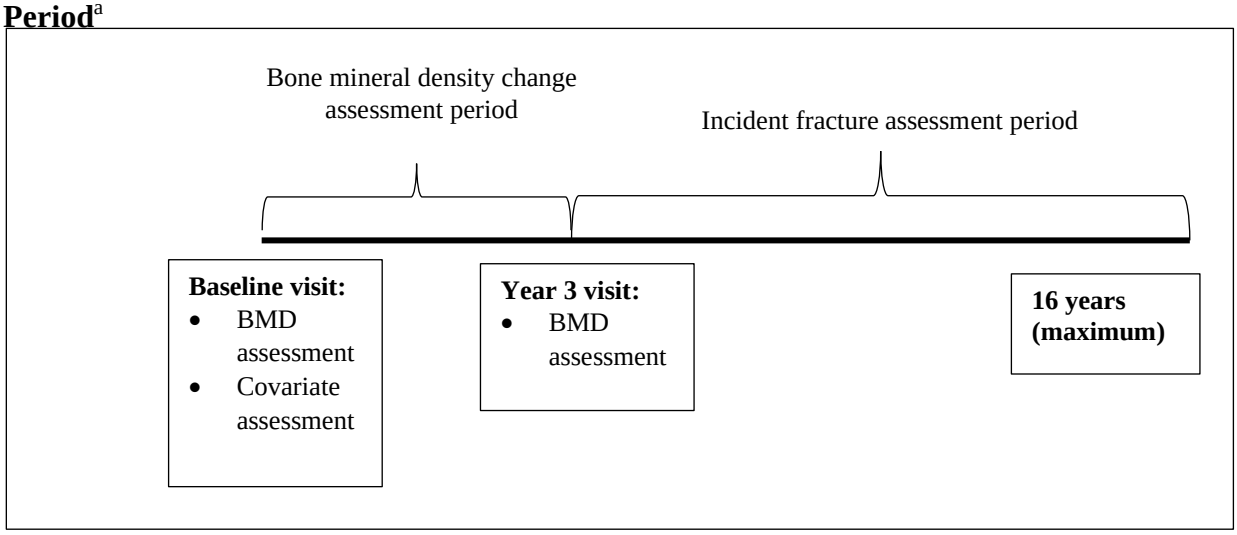
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. STROBE Analytic Sample Flow Diagram



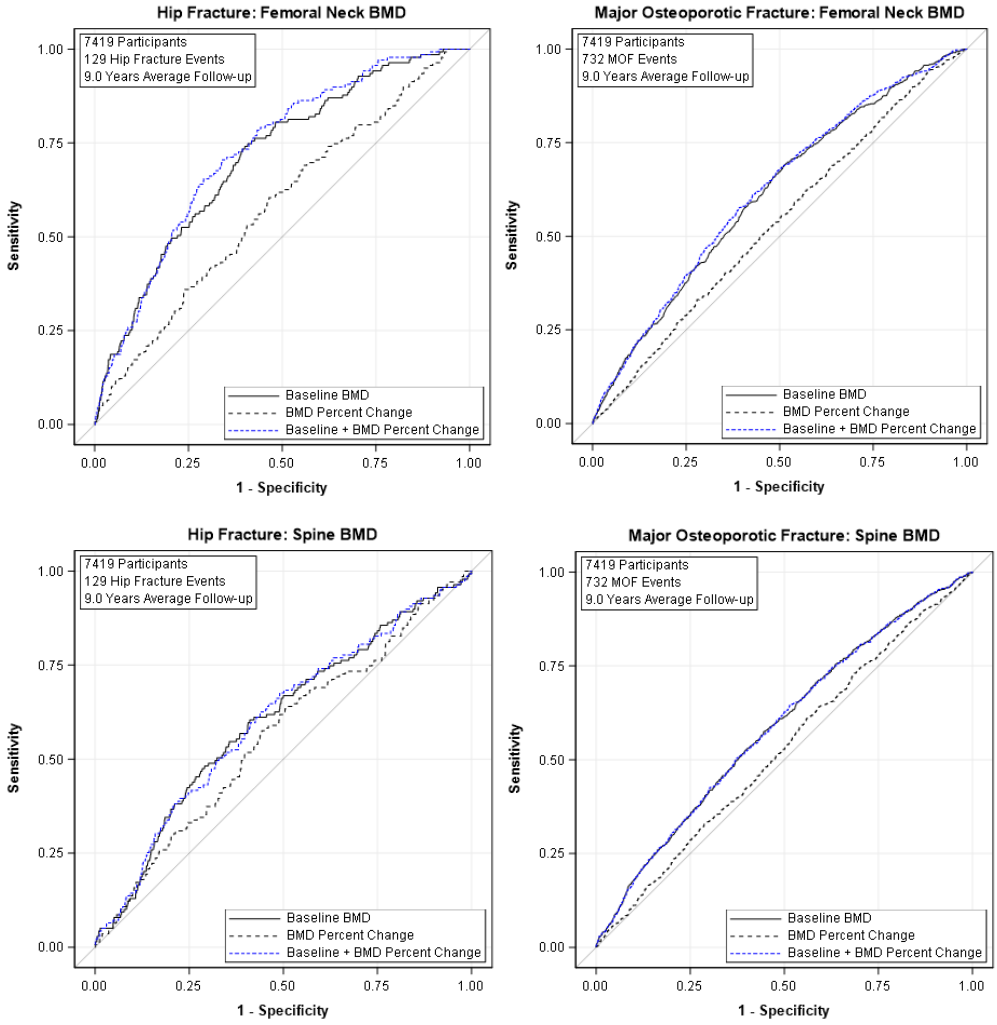
[1] Hip, spine, lower arm/wrist, upper arm/shoulder
[2] Hormone use, history of fracture, body mass index

eFigure 2. Bone Mineral Density Change Period in Relation to the Fracture Follow-up Period[a]



[a] Mean follow-up duration was 12 years from baseline.

eFigure 3. Receiver Operating Characteristic Curves for Femoral Neck BMD and Lumbar Spine BMD in Discrimination of Hip Fracture and Major Osteoporotic Fracture[a]



[a] BMD denotes Bone Mineral Density

eTable 1. Numbers of Hip and Major Osteoporotic Fracture Events During Follow-up

Study phase	n	Hip Fracture Events	Incident Major Osteoporotic Fracture Events[a]					
			Overall	*Hip*	*Lower Arm / Wrist*	*Upper Arm*	*Spine*	*Multiple Sites*[b]
Initial analytic sample	*9304*	*211*	*1196*	*186*	*483*	*295*	*216*	*16*
Participants reporting bone drug use on or before year 3	8461	185	1069	164	449	248	198	10
Participants with no follow-up after year 3	8445	185	1068	164	448	248	198	10
Participants with prevalent osteoporotic fracture at study baseline	8111	174	988	154	407	229	189	9
Participants with incident osteoporotic fracture before Year 3	7908	148	785	134	292	200	152	7
Missing covariate data	7419	139	732	127	271	182	145	7
Final analytic sample	*7419*	*139*	*732*	*127*	*271*	*182*	*145*	*7*

[a] Only the first major osteoporotic fracture site is counted for each participant
[b] Participants had fractures at multiple major osteoporotic fracture sites at the same time

eTable 2. Association of Annualized Absolute Bone Mineral Density (BMD) Change With Risk of Hip Fracture and Risk of Major Osteoporotic Fracture[a]

		Hip Fracture		Major Osteoporotic Fracture	
BMD Site		*1 SD Decrease*		*1 SD Decrease*	
Femoral Neck	*Baseline BMD[b]*	*HR (95% CI)* 1.79 (1.42, 2.26)	*p-value* <0.001	*HR (95% CI)* 1.51 (1.37, 1.67)	*p-value* <0.001
	Absolute Change	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	1.24 (1.05, 1.46)	0.01	1.11 (1.03, 1.20)	0.006
	Adjusted Adjusted + BMD	1.23 (1.03, 1.47) 1.33 (1.10, 1.61)	0.02 0.003	1.11 (1.03, 1.20) 1.18 (1.09, 1.28)	0.005 <0.001
Lumbar Spine	*Baseline BMD*	*HR (95% CI)* 1.15 (0.96, 1.37)	*p-value* 0.12	*HR (95% CI)* 1.39 (1.28, 1.51)	*p-value* <0.001
	Absolute Change	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	1.08 (0.91, 1.29)	0.36	1.05 (0.97, 1.13)	0.22
	Adjusted Adjusted + BMD	1.19 (0.99, 1.43) 1.19 (0.99, 1.44)	0.07 0.07	1.11 (1.03, 1.20) 1.12 (1.04, 1.21)	0.006 0.004

[a] hazard ratio; CI: confidence interval. For change in BMD, 1 SD decrease in absolute BMD corresponded to: 0.011372 g/cm2 at the total hip, 0.011696 g/cm2 at the femoral neck, and 0.016676 g/cm2 at the lumbar spine. Adjusted models are stratified by current hormone use (Yes/No) and Women's Health Initiative Study component (Clinical Trial/Observational Study) and adjusted for age, race/ethnicity, history of fracture, physical activity, body mass index, physical function, falls in the last year, and, in BMD-adjusted models ("Adjusted + BMD"), baseline BMD.

[b] HR per 1SD lower baseline BMD

eTable 3. Association of Annualized Absolute Bone Mineral Density (BMD) Change With Risk of Hip Fracture and Risk of Major Osteoporotic Fracture After Exclusion of Participants Taking Bone-Active Medications[a]

		Hip Fracture		Major Osteoporotic Fracture	
BMD Site		*1 SD Decrease*[1]		*1 SD Decrease*	
Total Hip	*Baseline BMD*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	2.57 (1.91, 3.47)	<0.001	1.87 (1.63, 2.14)	<0.001
	Adjusted[b]	1.66 (1.19, 2.31)	0.003	1.50 (1.29, 1.74)	<0.001
	Absolute Change	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	1.28 (0.99, 1.66)	0.06	1.12 (0.99, 1.27)	0.07
	Adjusted	1.10 (0.84, 1.42)	0.49	1.05 (0.92, 1.19)	0.46
	Adjusted + BMD	1.15 (0.88, 1.50)	0.30	1.09 (0.96, 1.24)	0.17
Femoral Neck	*Baseline BMD*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	2.58 (1.89, 3.53)	<0.001	1.89 (1.65, 2.18)	<0.001
	Adjusted	1.63 (1.16, 2.30)	0.005	1.51 (1.29, 1.76)	<0.001
	Absolute Change	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	1.11 (0.85, 1.44)	0.45	1.08 (0.95, 1.22)	0.24
	Adjusted	1.05 (0.79, 1.39)	0.75	1.07 (0.94, 1.22)	0.32
	Adjusted + BMD	1.09 (0.81, 1.46)	0.56	1.12 (0.97, 1.28)	0.12
Lumbar Spine	*Baseline BMD*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	1.36 (1.04, 1.79)	0.03	1.57 (1.37, 1.79)	<0.001
	Adjusted	1.05 (0.81, 1.36)	0.73	1.35 (1.18, 1.54)	<0.001
	Absolute Change	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
	Unadjusted	0.94 (0.72, 1.22)	0.63	1.01 (0.90, 1.15)	0.82
	Adjusted	1.06 (0.80, 1.40)	0.71	1.11 (0.97, 1.26)	0.12
	Adjusted + BMD	1.05 (0.79, 1.40)	0.72	1.11 (0.97, 1.27)	0.12

[a] bisphosphonates, teriparatide, denosumab, selective-estrogen receptor modulators, proton pump inhibitors, systemic corticosteroids, diabetes medications, selective serotonin reuptake inhibitors, loop diuretics, aromatase inhibitors) at any time during follow-up

[b] hazard ratio; CI: confidence interval. For change in BMD, 1 SD decrease in absolute BMD corresponded to: 0.011372 g/cm2 at the total hip, 0.011696 g/cm2 at the femoral neck, and 0.016676 g/cm2 at the lumbar spine. Adjusted models are stratified by current hormone use (Yes/No) and Women's Health Initiative Study component (Clinical Trial/Observational Study) and adjusted for age, race/ethnicity, history of fracture, physical activity, body mass index, physical function, falls in the last year, and, in BMD-adjusted models ("Adjusted + BMD"), baseline BMD.

eTable 4. Interaction of Annualized Absolute Bone Mineral Density (BMD) Change and Subgroups With Risk of Hip Fracture and Risk of Major Osteoporotic Fracture[a]

		Hip Fracture		Major Osteoporotic Fracture	
BMD Site	*Subgroup*	*1 SD Decrease[1]*	*Interaction*	*1 SD Decrease[1]*	*Interaction*
		HR (95% CI)[2]	*p-value[2]*	*HR (95% CI)[2]*	*p-value[2]*
Femoral Neck	Diabetes		0.04		0.81
	Yes	1.87 (1.29, 2.70)		1.20 (0.99, 1.46)	
	No	1.19 (0.96, 1.48)		1.17 (1.07, 1.28)	
	Age		0.78		0.15
	<65 years	1.75 (1.08, 2.85)		1.14 (0.99, 1.30)	
	65-74 years	1.10 (0.84, 1.45)		1.14 (1.01, 1.28)	
	≥75 years	1.56 (1.15, 2.11)		1.36 (1.15, 1.63)	
	Race		0.92		0.71
	African American	1.22 (0.51, 2.94)		1.10 (0.85, 1.42)	
	White	1.28 (1.04, 1.57)		1.15 (1.06, 1.26)	
	BMI		0.25		0.45
	<25	1.38 (1.01, 1.89)		1.20 (1.02, 1.40)	
	25-<30	1.71 (1.26, 2.33)		1.23 (1.07, 1.42)	
	≥30	1.01 (0.71, 1.42)		1.12 (0.99, 1.26)	
	Baseline T-Score		0.05		0.69
	≤ -2.5	0.96 (0.61, 1.50)		1.17 (0.91, 1.50)	
	> -2.5 - < -1.0	1.22 (0.95, 1.58)		1.18 (1.05, 1.32)	
	≥ -1.0	1.64 (1.25, 2.15)		1.13 (1.01, 1.28)	
	HT Use		0.95		0.33
	Yes	1.33 (0.96, 1.83)		1.24 (1.09, 1.40)	
	No	1.35 (1.07, 1.70)		1.14 (1.03, 1.27)	
Lumbar Spine	Diabetes		0.19		0.27
	Yes	1.54 (1.01, 2.33)		1.03 (0.86, 1.22)	
	No	1.12 (0.91, 1.39)		1.14 (1.05, 1.25)	
	Age		0.83		0.18
	<65 years	1.16 (0.72, 1.86)		1.04 (0.92, 1.18)	
	65-74 years	1.19 (0.91, 1.55)		1.13 (1.01, 1.27)	
	≥75 years	1.19 (0.88, 1.60)		1.20 (1.00, 1.43)	
	Race		0.22		0.28
	African American	0.73 (0.35, 1.52)		0.97 (0.76, 1.24)	
	White	1.17 (0.95, 1.43)		1.12 (1.03, 1.22)	
	BMI		0.79		0.37
	<25	1.05 (0.76, 1.47)		1.10 (0.93, 1.30)	
	25-<30	1.40 (1.06, 1.86)		1.25 (1.10, 1.43)	
	≥30	1.10 (0.78, 1.55)		1.04 (0.93, 1.16)	
	Baseline T-Score		0.65		
	≤ -2.5	1.14 (0.62, 2.09)		0.99 (0.82, 1.19)	
	> -2.5 - < -1.0	1.13 (0.87, 1.48)		1.19 (1.05, 1.35)	
	≥ -1.0	1.25 (0.95, 1.66)		1.12 (1.00, 1.24)	

[a] HR denotes hazard ratio; CI denotes confidence interval. HR, 95% CI, and interaction p-value were derived from a survival model with fracture outcome as a function of annualized absolute change in BMD, the subgroup of interest, and their interaction. Models are stratified by current hormone use (Yes/No) and Women's Health Initiative Study component (Clinical Trial/Observational Study) and adjusted for age (omitted from the models stratified by age), race/ethnicity, body mass index (BMI), history of fracture, and baseline BMD. For change in BMD, 1 SD decrease corresponded to: 0.011372 g/cm^2 at the hip, 0.011696 g/cm^2 at the femoral neck, and 0.016676 g/cm^2 at the lumbar spine. For age, BMI, and baseline BMD T-score subgroups, p-value is from a separate model testing interaction of annualized absolute change in BMD by trend over subgroup levels.

	HT Use	0.37	0.24
	Yes	1.07 (0.80, 1.45)	1.19 (1.05, 1.34)
	No	1.28 (1.01, 1.61)	1.08 (0.98, 1.20)

eTable 5. Comparison of Area Under the Curve of Models Adjusted For Baseline Bone Mineral Density (BMD), Absolute Yearly Change (g/cm2), or Their Combination, Overall and by Age Group, in Prediction of Incident Fracture[a]

Hip Fracture	**Baseline**	**BMD Change**	**Baseline + BMD Change**
BMD Site	*AUC (95% CI)*	*AUC (95% CI)*	*AUC (95% CI)*
Femoral Neck			
Overall	0.71 (0.67, 0.75)	0.58 (0.53, 0.63)	0.73 (0.69, 0.77)
<65	0.69 (0.57, 0.81)	0.63 (0.49, 0.77)	0.74 (0.61, 0.86)
65-74	0.66 (0.60, 0.73)	0.54 (0.47, 0.61)	0.67 (0.61, 0.73)
≥75	0.63 (0.56, 0.70)	0.60 (0.52, 0.68)	0.68 (0.62, 0.75)
Lumbar Spine			
Overall	0.60 (0.56, 0.65)	0.56 (0.51, 0.61)	0.60 (0.56, 0.65)
<65	0.58 (0.45, 0.71)	0.59 (0.45, 0.73)	0.58 (0.44, 0.72)
65-74	0.58 (0.52, 0.64)	0.55 (0.48, 0.62)	0.58 (0.52, 0.65)
≥75	0.58 (0.49, 0.66)	0.57 (0.50, 0.65)	0.59 (0.51, 0.67)
Major Osteoporotic Fracture	Baseline	BMD Change	Baseline + BMD Change
BMD Site	*AUC (95% CI)*	*AUC (95% CI)*	*AUC (95% CI)*
Femoral Neck			
Overall	0.61 (0.59, 0.63)	0.53 (0.51, 0.56)	0.62 (0.60, 0.64)
<65	0.59 (0.55, 0.62)	0.53 (0.49, 0.57)	0.59 (0.56, 0.63)
65-74	0.61 (0.58, 0.64)	0.54 (0.51, 0.57)	0.61 (0.58, 0.65)
≥75	0.60 (0.55, 0.65)	0.58 (0.53, 0.63)	0.63 (0.59, 0.68)
Lumbar Spine			
Overall	0.59 (0.57, 0.61)	0.53 (0.50, 0.55)	0.59 (0.57, 0.61)
<65	0.57 (0.54, 0.61)	0.51 (0.48, 0.55)	0.57 (0.54, 0.61)
65-74	0.59 (0.56, 0.62)	0.54 (0.51, 0.57)	0.59 (0.56, 0.62)
≥75	0.59 (0.54, 0.64)	0.55 (0.50, 0.60)	0.59 (0.54, 0.64)

[a] All logistic regression models are adjusted for current hormone use (Yes/No), Women's Health Initiative Study component (Clinical Trial/Observational Study), age, race/ethnicity, history of fracture, physical activity, physical function, and number of falls in the last year. Major osteoporotic fractures include: hip, spine, lower arm/wrist, upper arm/shoulder.